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ACTH versus Vigabatrin as First line Treatment for West Syndrome – A Prospective Study

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Abstract:

West syndrome represents a seizure disorder with unique clinical and electroencephalographic features. The association of spasm and developmental delay or stagnation with definite EEG changes defines West's syndrome.

The study was done to compare the efficacy of corticotropin (Inj ACTH, deep I/M 3 IU/kg/day) and Vigabatrin (50 mg/kg/day), in suppressing clinical spasms in untreated West Syndrome (WS). It was a randomized, prospective study done in Department of Pediatric Neurology and Development, BSMMU in 1 year period. Among sixty

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patients, group A was randomly given inj ACTH and group B was given oral Vigabatrin as per dose schedule. Among the patients 36(60%) were less than 3 months of age, 20(33%) children were in 3 to 6 month of age and 4 cases (7%) were in 6 to 9 month of age. Perinatal asphyxia was the commonest cause in both groups. In both groups abnormal findings of CT scan and MRI of brain were found in 78.3% cases and hypsarrythmia was the most common EEG finding. 31 patients were treated with ACTH and 29 with vigabatrin (VGB). Cessation of spasms was observed in 12 (41.37%) of the patients randomized to VGB and in 14 (51.61%) of those randomized to ACTH. In ACTH group 32% developed side effects while in VGB group 13 % developed side effects which were statistically significant. (p value < 0.05).

Conclusion: Our data support that Vigabatrin may be considered a as a first line drug giving emphasis to the response and decreased side effects.

Key words: West syndrome, ACTH, Vigabatrin

INTRODUCTION:

West syndrome (WS) represents a seizure disorder with unique clinical and electroencephalographic (hypsarrhythmia) features and a poor prognosis including chronic intractable epilepsy and psychomotor retardation. The association of spasm and developmental delay or retardaton with or without EEG changes defines WS .[1] The incidence of infantile spasm ranges from 0.25-0.6 per 1000 live births. [2]

Three key factor lead to the diagnosis. The first factor is age. Infantile spasm is a disorder of the developing nervous system and the spasms typically begin in the first year of life, most commonly between 4 and 8 months of age. The second factor is semiology. Clusters of flexion jerks of neck, trunk and extremities lasting 1-2 seconds are typical. [3] The third factor is

very distinct EEG pattern that is hypsarrhythmia which is a very high voltage disorganized pattern of EEG. [4]

The treatment of WS has been both a conundrum and a challenge for the pediatric neurologist as the entity appears to be resistant to many conventional antiepileptic drugs. Agents that have been employed in the treatment of infantile spasm include Adrenocorticotropic hormone (ACTH), Vigabatrin, Corticosteroids, Nitrazepam, Sodium valproate, a ketogenic diet, vitamin B6, intravenous gammmaglobin and Zonisamide. [2, 5]

Currently ACTH and vigabatrin are the actively investigated drugs with some evidence of efficacy in the treatment of infantile spasm. However there is little consensus with the regards to the definitive dose, efficacy or duration of treatment of these agents in comparison to each other. [6] Studies on experience with ACTH and Vigabatrin from Bangladesh is lacking. Therefore this study was designed to provide an important perspective on the treatment of WS in the setting of developing country like Bangladesh.

METHODOLOGY:

It was a randomized, prospective, double blind study done in Department of Pediatric Neurology and Development, Bangabandhu Sheikh Mujib Medical University, Dhaka. The study duration was one year. The objective was to compare the efficacy of corticotropin (Inj ACTH, deep I/M 3 IU/kg/day) and Vigabatrin (50 mg/kg/day), as starting dose, in suppressing clinical spasms in children previously not treated with hormone treatment (ACTH, Prednisolone) or vigabatrine.

Patient population consisted of consecutive sixty infants fulfilling entry criteria, including the presence of clinical spasms, hypsarrhythmia or variants during a full sleep cycle EEG, and no prior steroid/ACTH/ vigabatrin treatment. Infants

were admitted in the hospital after diagnosis and were enrolled for the study. Diagnosis was done on the basis of **ILAE, 1989, International Classification of Epilepsy and Epileptic syndromes.**

A **spasm** is defined as very brief and tonic seizure lasting for a few seconds. **Clusters** were defined as a number of spasms ranging from a few to 100 with 3-30 sec interval between each spasm.[2] All cases were divided into three categories. Those cases in which infantile spasms occurred without any identifiable cause, other neurological signs or symptoms, considered as **idiopathic**. Patients who were suspected of being symptomatic but for whom an underlying structural or biochemical cause could not be identified were classified as **cryptogenic**. Cases were considered as **symptomatic** when the infantile spasms resulted from an identifiable cause and often where neurological features or unequivocal developmental delay preceded the onset of symptoms. [7]

Before enrollment an informed written consent was taken from guardian of all children. Ethical clearance was taken from the institutional review board (IRB). Then any of the allocated medication was given as per randomization group. Computer generated randomization was done.

ACTH was given as per the following schedule-

All cases of infantile spasm Inj ACTH, deep I/M -3 IU/kg/day in week 1 and 2. Then for the following weeks ACTH was given in the following way-

a. **Cryptogenic responder:** 1.5 IU/kg/day in week 3and 0.75 IU/kg/day in week 4.

b. Symptomatic **responder:** 3 IU/kg/day in week 3 and 4, 1.5 IU/kg/day in week 5 and 0.75 IU/kg/day in week 6.

c. Cryptogenic and symptomatic nonresponder: 6 IU/kg/day in week 3 and 4 , 3 IU/kg/day in week 5,1.5 IU/kg/day in week 6 and 0.75 IU/kg/day in week 7.

Tab Hydrocontison was added as 1 mg/Kg/Day from 3rd week onward along with inj ACTH.

As ACTH has some serious side effects each patient having ACTH were admitted for whole period and followed up daily for **temperature, heart rate, blood pressure, body weight**. At **4th day of admission** the following investigations were done, **complete blood count, Liver function test, Random blood sugar, serum electrolyte and serum creatinin.** The pattern and number of spasm, side effects of ACTH and developmental milestones were followed up.

Tab Vigabatrin was started at the dose of **50mg/kg/day** in two divided dose which was increased up to **150 mg/kg/day** depending upon the response of the patient. It was be given for a period of **6 months** if there is no side effect .The patients of this group were admitted for minimum one week and then discharged. Then they were followed up for adverse effect after 1 week, 2 week, 1 month and then 3 monthly.

RESULT:

Baseline characteristics: The baseline characteristics of the patients are presented in the table 1. The majority of the patients are male (79.3%). The mean age of the patients were 9.16 in ACTH group and 10.89 in Vigabatrin group. In both group most of the patients developed spasm in less than 3 months (ACTH 61% and Vigabatrin 62%). In the patient population, symptomatic patients were prevailing (ACTH 87% and Vigabatrin 82.7%).

Table 1: Baseline Characteristics of children with WS

	ACTH n=31	VIGABATRIN n=29
MALE	17 (54.8%)	23(79.3%)
FEMALE	14 (45.2%)	6 (20.7%)
MEAN AGE (MONTHS)	9.16	10.89
AGE OF ONSET <3 MONTHS	19(61%)	18 (62%)
3-6 MONTHS	10(32%)	10(34.4%)
>6 MONTHS	2(3.2%)	1(3.4%)
SYMPTOMATIC	27(87%)	24(82.7%)
IDIOPATHIC	4(12.9%)	5(17.24%)

Table 1(cont) :Baseline Characteristics of children with WS.

S Seizures per Day	ACTH n=31	VIGABATRIN n=29
<10	12(38.70%)	17(58. 6%)
10-20	14(45.1%)	8 (27. 58%)
>20	5 (16.12%)	4(13.7%)

Etiology of WS: Among the symptomatic cases hypoxic ischemic encephalopathy due to perinatal asphyxia was identified as the leading cause of WS. It was seen that 58% infants of ACTH group and 62 % of the vigabatrin group had perinatal asphyxia. (Table 2)

Table 2: Etiology of symptomatic patients

Causes	ACTH n=31	VIGABATRIN n=29
HIE	18(58%)	18(62%)
NEONATAL SEIZURE	2(6.5%)	1(3.44%)
TORCH	1 (3.22%)	
HYPERBILIRUBINEMIA	1(3.22%)	1(3.44%)
NEURONAL MIGRATION DEFECT	1(3.22%)	1(3.44%)
NEONATAL SEPSIS/MENINGITIS	1(3.22%)	1(3.44%)
MULTIPLE	3(9.4%)	2(6.88%)

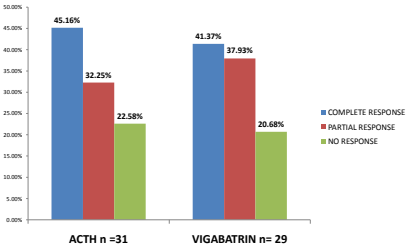
EEG and neuroimaging characteristics: All the patients received an initial EEG. Classical hypsarrythmia was the commonest finding in the EEG (ACTH group 58.06% and vigabatrin group 55.1%). CT scan or MRI of the brain revealed most of the patients had abnormal imaging. (Table 3) .

Table 3: EEG and Neuroimaging characteristics

	ACTH n=31	VIGABATRIN n=29
EEG: HYPSARRYTHMIA	18(58.06%)	16(55.17%)
MODIFIED HYPSARRYTHMIA	4(12.9%)	4(17.24%)
MULTIFOCAL SPIKE	4(12.9%),	4(17.24%),
OTHERS	5(16.12%)	5(10.34%)
NEUROIMAGING(CT/MRI)		
NORMAL	5(16.12%)	7(24.13%)
ABNORMAL	22(70%)	21(72.41%)
NOT DONE	4(12.90%)	1(3.44%)

Treatment and outcome: All patients were given one medication at any given time. The result of the initial therapy is given in table 4.

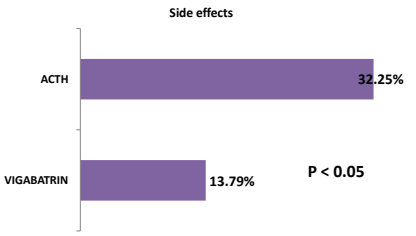
Table 4: Response of patients to therapy



Side effects of therapy: Comparing the side effect profile of the drugs 32.25 of the patients in ACTH group developed one or more side effects while only 13% of the vigabatrin group

developed side effects. Due to side effects, 2 patients of ACTH group could not complete the complete schedule.

Table 5: Side Effects of Drugs



DISCUSSION:

This was a prospective study of children with WS conducted in resource-constrained settings. This study highlights the clinical spectrum, etiology and treatment response in children with WS, hence providing a developing country perspective. It was observed that symptomatic WS formed a major group in the children studied.

The study comprised of larger number of patients compared with most of the other studies; 26 children by Sharma and Vishwanathan,[8] 47 children by Matsuo et al,[9] and 28 children by Goldstein and Slomski.[10] A striking male preponderance was observed in this study. The male dominance is similar to other studies from the neighboring countires.[11, 12] The mean age of presentation of patients to us (ACTH 9.16 months and vigabatrin 10.89 months) was reasonably late as the age of onset of seizure was much earlier. This is because majority of our study population is illiterate and preference of traditional medicine is still persisting. Moreover, the type of the seizure is often mistaken with other nonepileptic phenomenon like startling. The late presentation has also been observed in other related studies in the subcontinent. [13]

Majority of the children were symptomatic in our study. Symptomatic infants also predominated in other related studies in the developing countries. [11, 12.13] It is to be noted that the proportion of symptomatic cases is higher as compared to western data. In the United Kingdom infantile spasms study, a known etiology could be demonstrated in 61% of the cases, whereas in our study, known etiology was found in 87% and 82.7 % in ACTH and vigabatrin group respectively.[14] The most common cause of WS in this study was hypoxic ischemic encephalopathy due to perinatal asphyxia. This may be reflection of the unhealthy existing perinatal service and subaverage maternal care. The data is different in the studies of the western countries. Prenatal causes like cortical malformations, neurocutaneous syndromes, and genetic–metabolic disorders are the predominant etiologies in the West. [1, 14, 15]

Classical hypsarrythmia was the most common finding in EEG in both group in this study. Other types of EEG were modified hypsarrythmia and multifocal spikes. Findings were similar to other studies where classic hypsarrhythmia was the most common finding in the EEG.[16]

Cessation of spasms was observed in 12 (41.37%) of the patients randomized to Vigabatrine and in 14 (51.61%) of those randomized to ACTH. In a similar study the complete cessation was found in 55% and 50% patients treated with vigabatrine and inj ACTH respectively. Here majority of the patient who responded to treatment did so within the first few weeks of being put on therapy. [16] However, some studies showed better response to ACTH, about 70% of complete remission. [17,18,19] Regarding this study, time to response in vigabatrin treated children was observed in less than 1 week among 13(44.82%) infants. On the other side, response to ACTH was observed within 1 week among 13 (41.93%) children. A full 2 weeks of therapy was allowed in this study before switching to other

drug. No statistically significant difference was observed between the response rates of patients put on either ACTH or vigabatrin therapy. In the United Kingdom infantile spasms study, spasm freedom was achieved in 76% of children taking ACTH (40 IU/alternate day) and 54% in children treated with vigabatrine. [20]

Regarding the side-effect profile, Vigabatrin was better than ACTH; with only 4(13.79%) patients experiencing the adverse effects, as opposed to ACTH, where 10(32.25%) patients reported adverse effects. Among the side effects in ACTH treated children, 7 patients had hypertension, 3 patients had severe irritability and 1 patient had pigmentation (this patient also had hypertension). The predominant side effect in vigabatrine group was irritability (2) and dystonia (2). A previous study has reported arterial hypertension in 11 out of 162 children (6.8%) on ACTH therapy. [21]Our study also resembles the study by Vigevano and Cilio who reported hormonal treatments have greater adverse effects and thus a higher potential to induce mortality . [22]

CONCLUSIONS:

In this study the efficacy of vigabatrin was comparable to ACTH in treating both the symptomatic and the idiopathic type of WS. However, vigabatrin had better tolerability than ACTH. We also studied the clinical and etiological aspects of WS which showed perinatal asphyxia was the commonest cause identified, thus it will highlight the necessity of improvisation of perinatal care.

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